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Original Research Article

MASCC vs CISNE SCORES COMPARISON IN FEBRILE NEUTROPENIA: Which is better?

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ABSTRACT

Background: The Multinational Association for Supportive Care in Cancer (MASCC) and Clinical Index of Stable Febrile Neutropenia (CISNE) scores are validated for risk stratification in the febrile neutropenia patients. Both these scores have advantages and limitations. This study was conducted to compare the MASCC and CISNE scores with respect to their ability to assign accurate risk stratification and predict outcomes.

Materials and Methods: This is a hospital-based prospective study included all-comers fulfilling the eligibility criteria from January 2018 till October 2019. In addition to demographic data, clinical data were obtained prospectively regarding clinical deterioration requiring up-gradation in treatment or death. Both MASCC and CISNE scores were calculated for all the patients and each patient was risk stratified as per the two different scores. Patients could be discharged once there were afebrile and after count recovery and were followed up to 30 days post discharge.

Results: A total of 96 febrile neutropenia episodes were included in the study (Total of 92 patients, with 4 patients with a repeat episode of febrile neutropenia). Mean age of the study population was 35 years (range 4 to 75 years). Total 58 (60.42%) episodes were in solid tumors and 38 (39.58%) were in hematological malignancies. With MASCC febrile neutropenia risk index, 63 (65.63%) were low risk and 33 (34.38%) were high risk. With CISNE, 7 (7.29%) were low risk, 72 (75%) were intermediate risk and 17 (17.71%) were high risk. When calculated with MASCC, 15 out of 33 episodes (45.45%) in high risk episodes required upgradation in the level of care and 18 out of 63(28.57%) episodes in low risk episodes required upgradation in the level of care. Whereas with CISNE 8 out of 17(87.5%) episodes in high risk required upgradation in the level of care and 25 out of 72 (34.72%) in intermediate risk required upgradation in the level of care, while none of the low risk required upgradation in the level of care. None of the low risk in CISNE experienced death. In MASCC low risk subset 1 out of 63(1.68%) died. Both MASCC and CISNE predicted outcomes of the febrile neutropenia episode accurately.

Conclusion: Both CISNE and MASCC has reasonable discriminatory value in predicting the outcome, however CISNE performed better compared to MASCC in both low and high-risk subsets.

Keywords: CISNE, MASCC, Neutropenia, Hemotological Malignancies.

INTRODUCTION

Neutropenia is a potentially life-threatening toxicity that predisposes patients with cancer to serious infections and limits the optimal delivery of therapeutic doses. Febrile neutropenia (FN) is a common complication of cancer chemotherapy. It is defined as an oral temperature of > 38.50C (1010F) or two consecutive >380C (100.40F) for two hours and an absolute neutrophil count(ANC) of < 500cells/mm3 or expected to fall below 500/mm3

within 48 hours.[1] A study across inpatient and outpatient care settings demonstrated a 16.8% risk of developing FN during a course of chemotherapy.[2]

In addition to the severity of neutropenia, the duration of neutropenia is also an important determinant of both the infection risk and infection type. Mortality rates approach 5% and 11% in patients with solid tumors and hematological malignancies, respectively.[3] Various prognostic tools have been created to risk-stratify patients with neutropenic fever.

Talcott score was the first validated and widely adopted score to identify the low risk cohort in patients with febrile neutropenia.[4] Later, The Multinational Association for Supportive Care in Cancer (MASCC) score was developed by Klastersky J et al,[5] for identifying low risk febrile neutropenia patients and more recently, the Clinical Index of Stable Febrile Neutropenia (CISNE) score has been formulated by Carmonas-Bayonas et al.[6]

The MASCC score (TABLE-1) is based upon disease burden, clinical instability, age, and comorbid condition, and has been validated and recommended in most of the neutropenic fever guidelines. A score of ≥21 was recommended as the threshold for low risk. The MASCC score was considered as more sensitive but with similar specificity when compared to the Talcott score, leading to its world-wide acceptance.[5]

The CISNE (Table -2) score is based on clinical instability, laboratory data, and comorbid conditions, and has been validated mainly in solid malignancies. CISNE score stratifies patients with febrile neutropenia into low, intermediate, and high risk and is reported to have increased specificity and positive predictive value in the identification of low-risk febrile neutropenic patients.[7] These low risk patients can be safely managed in outpatient setting with broad spectrum oral antibiotics. Accurate identification of this low risk subset avoids overtreatment, nosocomial infections, as well as burden on health care system.

This study was conducted to assess the widely established MASCC score, and the relatively newer CISNE score with respect to risk stratification, diagnostic accuracy, and outcomes.

MATERIAL AND METHODS

This is a hospital-based prospective study done in the Department of Medical Oncology at a tertiary care hospital from Jan 2018 till October 2019 after obtaining the approval of the Institutional Ethics Review board. Patients who met the definition of febrile neutropenia, that is; oral temperature of > 38.50C (1010F) or two consecutive >380C (100.40F) for two hours and an absolute neutrophil count (ANC) of < 500cells/mm3 or expected to fall below 500/mm3 within 48 hours were included after obtaining informed consent. Patients were excluded if their neutropenia was considered unrelated to chemotherapy and patients with hematological malignancies receiving induction chemotherapy.

Clinical data for each patient was obtained including age, sex, existing comorbidities, burden of symptoms, type of malignancy, chemotherapy regimen received, prophylactic growth factor support, the degree of neutropenia, the focus of infection, cultures, patient management (including inpatient/outpatient, route of antibiotics) and clinical deterioration requiring up gradation in treatment, or leading to death.

Burden of symptoms was classified as either mild, moderate, or severe. Symptoms that were barely noticeable and not interfering with performance of daily activities were considered as mild. If the symptoms made the patient uncomfortable and had a negative influence on the daily activities, they were considered as moderate. The symptoms were classified as severe if they led to severe discomfort and severe limitation on performance of daily activities.[8]

Clinical deterioration was defined as a new development of acute organ failure (laboratory or clinical evidence of acute renalfailure, liver failure, heart failure, or respiratory failure), onset of hypotension, or development of any other disease process that necessitated an acute change in clinical management.[8] Clinical stability was defined as absence of organ dysfunction, abnormalities in vital signs, and major infections.[7]

Upgradation in the level of care, was defined as any escalation of antibiotics, requirement of inotropes, requirement of oxygen or ventilator support after admission.[8] Both MASCC and CISNE scores were calculated for all the patients and they were risk stratified as per both scores (Table 1 & 2).

We included all patients with FN irrespective of solid or hematological malignancies and all risk categories. All patients irrespective of risk status were admitted and all of them received IV antibiotics as per our Institute protocol, as there was no access to emergency medical care in case of deterioration for most patients.

Patients were discharged once they were afebrile and after count recovery. Patients were followed up to 30 days post discharge. Primary objective of the study was to compare the risk scores with the outcome.

Sample Size Calculation

The study by Coyne et al,[8] has revealed that the CISNE score identified 23% of the cases as low risk cohort as compared to MASCC which identified 54.2% as low risk cohort. Based on the above findings of the study with a relative risk (RR) of 2.4 and precision for RR at 10% and desired CI of 95% it is estimated that minimum of 94 episodes of febrile neutropenia need to be included for the study. The sample size was estimated employing N master software developed by Department of Biostatistics resource and training center, CMC, Vellore.

Statistical Analysis

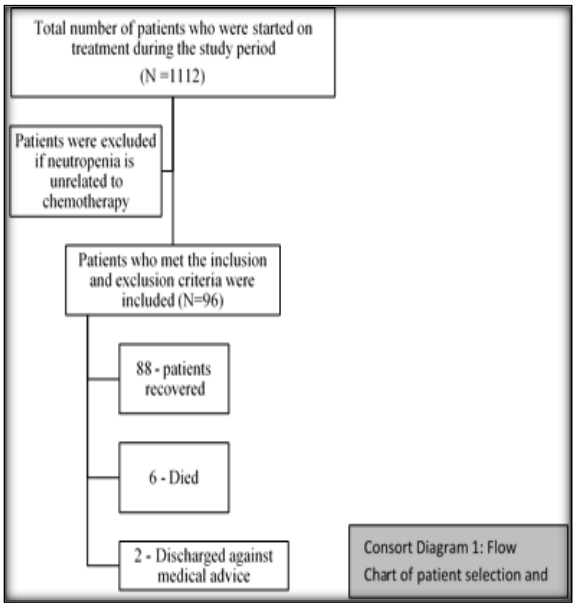
Diagnostic validity indicators such as sensitivity, specificity, positive predictive value, and negative

predictive value were estimated for outcomes for CISNE and MASCC. Diagnostic accuracy was calculated for outcomes and was defined as the ability of a test to detect a condition when it is present and detect the absence of a condition when it is absent. In order to evaluate the inter-reliability agreement in the determination of low risk by both the scoring methods a Cohen's K value were estimated. Further descriptive statistics such as mean and standard deviation or median with interquartile range were estimated for quantitative factors such as age, duration of disease etc. Association of various qualitative variables were studied by Chi Square test of significance. Chi Square test for goodness of it were used to measure the association between the MASCC and CISNE with outcome, $P<0.05$ considered as statistically significant.

RESULTS

In the given study period, a total of 1112 patients were started on chemotherapy at our Institute and out of which a total of 96 (8.63%) who developed febrile neutropenia were included in the study after informed consent (Consort diagram 1).

Total of 92 patients were included in our study, and 4 patients had a second episode of febrile neutropenia adding the total to 96 episodes. All the results and risk stratification, hence forth, will be discussed according to the febrile neutropenia episodes (N-96).



Fifty-eight out of 880 patients (5.8%) receiving treatment for solid tumors developed FN; while 38 out of 232 patients (16.37%) developing FN had hematological malignancies. Majority of the episodes in solid tumors were seen in those diagnosed with osteosarcoma (12.06%). While 84 (87.50%) of patients had grade 4 neutropenia, 12 (12.50%) had grade 3 neutropenia.

The baseline characteristics of the patients in the study are depicted in Table-3. Median age of the study population was 38 years (range 4 to 75 years). Co-morbidities such as diabetes, hypertension, ischemic heart disease and COPD were present in 23 (24%) of patients.

Prophylactic growth factor was received prior to FN in 46 (47.92%) episodes and was not received in 50 (52.06%) FN episodes. When assessed at the time of admission, 51(53.13%) had moderate symptoms, 29 (30.21%) had mild symptoms and 16(16.67%) had severe symptoms. The differences between solid and hematological malignancies is depicted in Table 4.

Source of infection could be identified in only 28 (29.16%) FN episodes. Blood culture was positive in 22 (22.91%) episodes out of which, 16 (72.72%) were gram negative and remaining 6 (27.27%) were gram positive, with Pseudomonas aeruginosa being the most common organism among the gram-negative organisms (31.25%). Urine culture was positive for E. coli in 3(13.6%).

Clinical deterioration was noted in 12 (12.50%) episodes and total 33 (34.38%) episodes required upgradation in the level of care. Total 88 (91.67%) recovered, 6 (6.25%) died during the admission and 2 (2.08%) got discharged against medical advice. After 1 month of follow up 75 (84%) were stable, 4 (4%) lost to follow up & 3 (3%) were advised for best supportive care. There were 4 episodes of second febrile neutropenia within that 30 days of follow up and 3 episodes of non-neutropenic fever.

With MASCC febrile neutropenia risk score, 63 (65.63%) were categorized as low risk and 33 (34.38%) were high risk. With CISNE risk scoring, 7 (7.29%) were low risk, 72 (75%) were intermediate risk and 17 (17.71%) were high risk. When calculated with MASCC, 15out of 33 episodes (45.45%) in high risk required upgradation in the level of care and 18 out of 63(28.57%) episodes in low risk required upgradation in the level of care. Whereas with CISNE, 8 out of 17(87.5%) episodes in high risk required upgradation in the level of care and 25(34.72%) out of 72 in intermediate risk required upgradation in the level of care. None of the low risk required upgradation in the level of care. Total 6(6.25%) died among the study population. None of the low risk in CISNE experienced death. In MASCC low risk subset, 1 out of 63(1.68%) died (Table 5). When we compared the outcome (which could be recovery or death/discharge against advice) with the risk stratification both CISNE and MASCC predicted outcomes accurately (Table 6 and Table 7).

Diagnostic accuracy and sensitivity were higher for CISNE over MASCC, which was 84.04% vs 70.21% and 85.23% vs 69.32%, respectively. While MASCC was more specific than CISNE in identifying the risk subsets and regarding outcomes (83.33% vs 66.67%). PPV and NPV were 97.40% and 23.53% for CISNE and 98.39% and 15.63% for MASCC for outcomes (Table-8). When analyzed the same in patients under 18 years of age MASCC was 100% sensitive and 82.14% specific in predicting the outcomes.

Table 1: MASCC risk score	
Characteristics	**Score**
Burden of illness : no or mild symptoms	5
No hypotension (SBP* > 90mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematological with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia: moderate	3
Outpatient status	3
Age < 60 years	2
Risk stratification: *Low risk – Score ≥ 21* *High risk – Score < 21*	
**SBP – Systolic Blood Pressure*	

Table 2: CISNE score	
Variable	**Points**
ECOG-PS* ≥ 2	2
Chronic obstructive pulmonary disease	1
Chronic cardiovascular disease	1
Oral mucositis grade ≥ 2	1
Monocytes < 200/µL	1
Stress induced hyperglycemia	2
Risk stratification: *Low risk – 0 points* *Intermediate risk – 1-2 points* *High risk - ≥ 3 points*	
**ECOG-PS – Easter Cooperative Oncology Group Performance Score*	

Table 3 : Baseline Characteristics		Number of FN episodes (N-96)
Age (in years)	<20 20-60 >60	29 (30.21%) 50 (52.08%) 17 (17.71%)
Sex	Male Female	51 (53.13%) 45 (46.88%)
Comorbidities	Yes No	23 (24%) 73 (76%)
Type of Cancer	Solid Hematological	58 (60.42%) 38 (39.58%)
Burden of Illness	Mild Moderate Severe	29 (30.21%) 51 (53.13%) 16 (16.67%)
Prophylactic G-CSF*	Yes No	46 (47.92%) 50 (52.06%)
**G-CSF – Granulocyte – Colony Stimulating Factor*		

Table 4: Difference between Solid vs Hematological malignancies			
		Solid (N= 58)	**Hematological** (N= 38)
Burden of Disease	Mild Moderate Severe	14 (24.13%) 31 (53.44%) 13 (22.41%)	15 (39.47%) 20 (52.63%) 3 (7.89%)
Grades of Neutropenia	Grade 3 Grade 4	6 (10.34%) 52 (89.65%)	6 (15.78%) 32 (84.21%)
Clinical Deterioration	Yes No	5 (8.62%) 53 (91.37%)	7 (18.42%) 31 (81.57%)
Follow up	Discharge Death DAMA*	54 (93.10%) 3 (5.17%) 1 (1.72%)	34 (89.47%) 3 (7.89%) 1 (2.63%)
*DAMA – Discharge Against Medical Advice			

Table 5: Comparison of outcomes according to risk stratification					
	MASCC		**CISNE**		
	Low N=63	**High** N=33	**Low** N=7	**Intermediate** N=72	**High** N=17
Upgradation in level of care	18 (28.57%)	15 (45.45%)	0 (0%)	25 (34.72%)	8 (87.5%)
Recovered	61 (96.82%)	27 (81.81%)	7 (100%)	68 (94.44%)	13 (76.47%)
Death	1 (1.58%)	5 (15.15%)	0 (0%)	2 (2.77%)	4 (23.52%)

Table 6: Significance of MASCC risk stratification with outcome						
	Risk	**Outcome**			Total	P-Value
		Recovered	**Death**	**DAMA***		
MASCC	**Low**	61	1	1	63	0.028
	High	27	5	1	33	
	Total	88	6	2	96	
*DAMA – Discharge Against Medical Advice						

Table 7: Significance of CISNE risk stratification with outcome						
	Risk	**Outcome**			**Total**	**P-Value**
		Recovered	**Death**	**DAMA***		
CISNE	**High**	13	4	0	17	0.025
	Intermediate	68	2	2	72	
	Low	7	0	0	7	
	Total	88	6	2	96	
*DAMA – Discharge Against Medical Advice						

DISCUSSION

With recent advances in cancer therapy, ambulatory outpatient care has taken an important place in the management of cancer patients.[9–11] For majority of the solid tumors and for some hematological malignancies, chemotherapy is offered on a day care basis. Among the different side effects associated with chemotherapy, febrile neutropenia remains to be one of the most common and dreaded complications.[7] Febrile neutropenia not only increases the risk of mortality and morbidity, it also limits the administration of effective doses of chemotherapy. Hence effective management of chemotherapy induced complications, helps in successfully completing the planned treatment and hence better the outcomes.

In febrile neutropenia, identification of the low risk subset helps in reducing the burden of the patient and on the health care system as well.[12] This low risk subset can be managed with oral antibiotics.[13] However, they should have immediate access to health care. There are several published reports highlighting both the safety and efficacy of oral antibiotic therapy on outpatient basis to be comparable with inpatient management of the patients.[7,8,14]

The challenge till date is to identify stablepatientswho are unlikely to develop serious complications. Both MASCC and CISNE score were validated for use in febrile neutropenia to predict outcomes. Some of the variables included in the MASCC score have been implicated in the weakness of the model; like the burden of illness and dehydration which could be subjective and inpatient development of fever is rarely encountered in clinical practice. Few studies have even demonstrated low sensitivity with MASCC (15). CISNE score was validated for low risk stable febrile neutropenia patients especially in solid tumors and was designed to use in emergency department at admission.[15,16] Certain studies have demonstrated the usefulness of CISNE in patients with hematological malignancies and few were done in both low and high risk patients(14). Few studies have demonstrated that CISNE was more sensitive when used in acute settings.[17] MASCC score is highly sensitive in predicting poor outcomes but less specific, especially in case of solid tumors compared to hematological malignancies.[7]

Majority of the episodes in solid tumors were seen in those diagnosed with osteosarcoma (12.06%) which was similar to other studies.[19] Majority (87.50%) had grade 4 neutropenia in our study, which was expected. Like many other studies febrile neutropenia developed despite use of prophylactic growth factor in nearly half of patients.[19]

Blood culture positivity rate was 22.91% which was comparable to other studies.[20] Among the positive cultures 72.72% were by gram negative organisms which was the common trend noted in patients with febrile neutropenia.[21] Pseudomonas aeruginosa was the most common organism identified at our institute. The prevalence of different gram-negative organisms varies among different hospitals.[22] Among 6 patients who died in our study, 5 had blood culture positive status. However, our study was not planned to calculate the significance between the two. Various studies report a wide range of mortality rate (7–33%) in FN patients.[23] The overall mortality rate in our study was 6.25% which was similar to other studies.[1,3]

With MASCC risk index, 65.63% were low risk and 34.38% were high risk. With CISNE, majority (75%) of the episodes were intermediate risk, which was contributed by mainly by the monocyte count. We noticed that if monocyte count was not a variable, majority of them would be in low risk category. With CISNE, 17.71% of episodes were high risk which was almost half when compared with MASCC. The identification of low risk subset with both CISNE and MASCC were comparable to other studies.[7]

Almost half of the patients (45.45%), categorized as high risk and 28.57% categorized as low risk with MASCC required up gradation in the level of care. Whereas with regard to CISNE risk stratification, majority (87.5%) of the high-risk patients and 34.72% categorized as intermediate risk required up gradation in the level of care. Also, none of the patients in the low risk group with CISNE score required any up gradation in the level of care. Even though the upgradation in the level of care with risk categorization was not statistically significant in our study, we noticed that CISNE predicted better in terms of requirement in the upgradation of level of care. Majority (91.67%) recovered and got discharged after recovery. Out of the total 6 deaths, none of them were in the low risk category with CISNE score and only 1 patient was from low risk category with MASCC score.

With both CISNE and MASCC scoring systems risk ability to predict need for upgradation of care was statistically significant (p=0.028, and p=0.025, respectively). In terms of diagnostic accuracy (84.4% vs 70.21%) and specificity (85.23% vs 69.32%) CISNE scoring system has higher score compared to MASCC scoring system whereas MASCC scoring system is more sensitive (83.33% vs 66.67%) in predicting upgradation of care.

Like other published reports our study also showed that both the scoring systems MASCC and CISNE have significant role in term of risk stratification; however, the individual systems have their own strengths and weakness regarding specificity and sensitivity.[7,8] Like our findings several other studies also documented high sensitivity and low specificity for MASCC and high specificity for CISNE for clinical course prediction.[7,8,14]

Ahn S et al, conducted a similar study and they compared retrospectively the MASCC and CISNE scores for identifying low risk febrile neutropenia patients in three tertiary care hospitals in the USA, UK, and South Korea, presenting at the emergency

department through pooled analysis. Similar to our study, Ahn S et al found that both the scoring systems have significant and comparable discriminatory value in predicting low risk in chemotherapy induced febrile neutropenia patients (7). However, in our study we found that the CISNE scoring system performed better in predicting both high risk and low risk compared to the MASCC.

Another retrospective study carried out by Coyne CJ et al, compared the accuracy of the two scoring systems, MASCC and CISNE in identifying low risk febrile neutropenia patients in Emergency Department. This study also documented that although both the scoring systems can predict risk stratification significantly accurately, CISNE is highly specific in identification of low risk febrile neutropenia patients.[8] In this study, CISNE scoring system showed higher NPV (98.1%) compared to MASCC (84%) and lower PPV (32.8%) compared to MASCC (52.5%). Similarly, in our study, CISNE scoring system (97.40%) showed higher NPV and lower PPV (23.53%) compared to MASCC scoring system (98.39% and 15.63%, respectively) regarding identification of risk groups.

Majority of the studies done previously, like those described before, were retrospective studies.[7,8] The strength of this study is that it is a prospective study and all of them were followed up for 1-month post discharge and could have helped in predicting the outcomes better.

>Since this was a prospective study the data and outcome analysis are likely to be more accurate unlike many other studies. We admitted all patients irrespective of their risk status as predicted by CISNE and MASCC scores, as majority of the patients do not have access to emergency medical facility when required and all the patients once admitted had received intravenous antibiotic which may have altered the outcome and one may consider this a limitation of the study. However, both scoring systems accurately predicted outcomes in our study.

In our study we found that both CISNE and MASCC were useful in predicting the outcomes; however, CISNE performed better compared to MASCC in both low and high-risk subsets.

CONCLUSION

Both the scoring systems MASCC and CISNE, have significant role in risk stratification in chemotherapy induced febrile neutropenia patients CISNE performed better with respect to outcome for both high risk and low risk patients. This study gives additional credence to the fact that both scores if used in combination in the emergency department may be able to truly identify low risk patients.

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